Claims

1. A method for obtaining a cell population enriched in antigen-specific T cells, comprising the steps of:

a) obtaining a mixed population of cells comprising T cells;

b) exposing the cell population to at least one antigen under conditions effective to elicit antigen-specific stimulation of at least one T cell and allowing expression of at least one product by the stimulated T cell, wherein the product is secreted in response to antigen stimulation;

c) modifying the surface of the cells to contain a capture moiety specific for the product such that the capture moiety is coupled to the cell surface;

d) culturing said population under conditions wherein said product is secreted, released and specifically bound to the capture moiety, thereby labeling the product-secreting cells; and

e) separating the cells according to the degree to which they are labeled with said product to obtain a population of cells substantially enriched in antigen-specific T cells,

wherein steps (b) and (c) can be performed in any order.

2. A method according to claim 1, further comprising the step of labeling the product prior to separation.

3. The method according to claim 2 wherein the product is labeled with a label moiety.

4. The method according to claim 3 wherein the label moiety is an antibody specific for the product.

5. The method according to claim 3 wherein the label moiety is fluorochromated and the separation is conducted by cell sorting.

6. The method according to claim 3 wherein the label moiety is magnetizable and the separation is conducted in a magnetic field of sufficient strength to magnetize the label moiety.

7. The method according to claim 6 wherein the label moiety comprises colloidal magnetic particles with a typical diameter of about 5 to 200 nm.

8. The method according to claim 1 wherein the capture moiety is an antibody or an antigen-binding fragment thereof.

9. The method according to claim 8 wherein the antibody or antigen binding fragment thereof is bispecific.

10. The method according to claim 1 wherein the coupling is through a lipid anchor attached to the capture moiety optionally through a linking moiety.

11. The method according to claim 1 wherein the coupling is through an antibody or an antigen-binding fragment thereof attached to the capture moiety, optionally through a linker.

12. The method according to claim 1 wherein the coupling is through direct chemical coupling of the capture moiety to components on the cell surface, optionally through a linker.

13. The method according to claim 9 wherein the coupling is through specific binding of the antibody to the cell.

14. A method to label antigen-specific T cells with a product secreted and released by the cells, wherein the product is secreted in response to antigen stimulation, which method comprises:

exposing the cells to at least one antigen under conditions effective to elicit antigen-specific stimulation of at least one T cell; and

modifying the surface of the cells to contain a capture moiety specific for the product; and

culturing the cells under conditions wherein the product is secreted, released and specifically bound to the capture moiety, thereby labeling the product-secreting cells.

15. The method according to claim 14 wherein the product is labeled with a label moiety.

~~16~~ 3. The method according to claim ~~15~~ 2 wherein the label moiety is an antibody.

~~17~~ 4. The method according to claim ~~14~~ 1 wherein the capture moiety is an antibody or an antigen-binding fragment thereof.

~~18~~ 5. The method according to claim ~~17~~ 4 wherein the antibody is bispecific.

19. The method according to claim 14 wherein the coupling is through a lipid anchor attached to the capture moiety optionally through a linker moiety.

20. The method according to claim 14 wherein the coupling is through an antibody or an antigen-binding fragment thereof attached to the capture moiety optionally through a linker.

21. The method according to claim 18 wherein the coupling is through specific binding of the antibody to the cell.

22. A composition obtained from the method according to claim 21.

23. The composition according to claim 21 wherein the capture moiety is an antibody or an antigen-binding fragment thereof.

24. The composition according to claim 23 wherein the antibody is bispecific.

25. The composition according to claim 22 wherein the coupling is through a lipid anchor moiety attached to the capture moiety optionally through a linking moiety.

27. The composition according to claim 22 wherein the coupling is through an antibody or an antigen-binding fragment thereof attached to the capture moiety, optionally through a linker.

28. The composition according to claim 25 wherein the coupling is through specific binding of the antibody to the cell.

29. Cells and progeny thereof separated according to the method of claim 1.

30. Cells separated according to the method of claim 1.

31. A method of analyzing a population of cells to identify or enumerate antigen-specific T cells that secrete and release an amount of product relative to other cells in the population, wherein the product is secreted in response to antigen stimulation, the method comprising the steps of:

labeling the cells by the method according to claim 14,

labeling the cells with at least one additional label that does not label the captured product, and

detecting the amount of product label relative to the additional label.

32. A method of determining a distribution of secretory activity in a cell population enriched in T cells, the method comprising the steps of:

labeling cells by the method according to claim 14, and

determining the amount of product label per cell, wherein the product is secreted and released in response to antigen stimulation.

33. The method according to claim 14 further comprising the steps of:

determining the amount and type of product label per cell wherein distribution of secreted product type and secretory activity for each secreted product type in a population of cells is determined.

34. A method for identifying antigen-specific T cells secreting and releasing at least one product in response to antigen stimulation, comprising the steps of:

combining a mixed population of cells enriched for T cells with at least one first, bispecific, antibody, each antibody having combining sites specific for a cell surface molecule and at least one product;

exposing the cell population to at least one antigen under conditions effective to elicit antigen-specific stimulation of at least one T cell;

incubating the combination under conditions and for a time sufficient to allow the cells to secrete the at least one product;

adding at least one label moiety; and

detecting the at least one label moiety.

Sub C12 35. The method according to claim 34 further comprising the step of separating the cells secreting the product from the mixed cell population.

36. The method according to claim 34 wherein the cell surface molecule is a naturally occurring cell surface protein.

37. The method according to claim 36 wherein the protein is a cell surface marker.

Sub C13 38. The method according to claim 37 wherein the cell surface molecule is selected from the group consisting of CD2, CD3, CD4, CD5, CD8, CD11b, CD26, CD27, CD28, CD29, CD30, CD31, CD38, CD40L, CD45RO, CD45RA, LAG3, T1/ST2, SLAM, Class I MHC molecules, Class II MHC molecules, T cell antigen receptor, and β_2-microglobulin.

39. The method according to claim 34 wherein the incubation conditions include a high viscosity or gel forming medium.

40. The method according to claim 34 wherein the label moiety is an antibody.

41. The method according to claim 40 wherein the antibody comprises a detectable label.

Sub C4 42. The method according to claim 41 wherein the label is selected from the group consisting of fluorophores, radioactive isotopes, chromophores and magnetic particles.

43. The method according to claim 40 wherein the label moiety is detected by fluorescence activated cell sorting.

44. The method according to claim 43 wherein the label moiety is detected by a third antibody.

45. The method according to claim 44 wherein the label moiety is coupled to digoxigenin and the third antibody is specific for digoxigenin.

46. The method according to claim 45 wherein the third antibody comprises a detectable label.

Sub C5 47. The method according to claim 46 wherein the label is selected from the group consisting of fluorophores, radioactive isotopes, chromophores, and magnetic particles.

48. The method according to claim 47 wherein the label moiety is detected by fluorescence activated cell sorting.

49. The method according to claim 34 wherein the label moiety comprises a magnetizable moiety.

50. The method according to claim 49 wherein the label moiety is detected by a third antibody coupled to a magnetizable moiety.

51. A method of treating a disease or condition related to a population of antigen-specific T cells comprising administering to an individual in need thereof an amount of a cell population enriched in antigen-specific T cells effective to treat the condition.

52. The method according to claim 51, wherein the condition is selected from the group consisting of an autoimmune disorder, graft rejection, and an allergic response.

53. The method according to claim 51, wherein the condition is a result of a lack of adequate control of the condition by antigen-specific T cells.

54. The method according to claim 53, wherein the condition is cancer.

55. The method according to claim 53, wherein the condition is an infection.

56. A kit for use in the detection of antigen-specific T cells that secrete a product in response to antigen stimulation, the kit comprising:

a product capture system comprised of at least one anchor moiety and at least one capture moiety; and

at least one label moiety.

57. The kit according to claim 56, wherein the capture moiety comprises at least one bispecific antibody having at least one antigen recognition site for at least one cell type and at least one antigen recognition site specific for the product.

58. The kit according to claim 57 wherein the at least one bispecific antibody and the at least one label moiety are in a single vial.

59. The kit according to claim 57 wherein the at least one bispecific antibody binds to the cell through a cell surface molecule.

60. The kit according to claim 57 wherein the cell surface molecule is a naturally occurring cell surface protein.

61. The kit according to claim 57 wherein the cell surface molecule is a cell surface marker.

62. The kit according to claim 61 wherein the cell surface molecule is selected from the group consisting of CD2, CD3, CD4, CD5, CD8, CD11b, CD26, CD27, CD28, CD29, CD30, CD31, CD38, CD40L, CD45RO, CD45RA, LAG3, T1/ST2, SLAM, Class I MHC molecules, Class II MHC molecules, T cell antigen receptor, and β_2-microglobulin.

63. The kit according to claim 55 wherein the incubation conditions include a high viscosity or gel forming medium.

64. The kit according to claim 63 wherein the medium is selected from the group consisting of gelatin, agarose, alginate and combination thereof,

65. The kit according to claim 57 wherein the label moiety is an antibody.

66. The kit according to claim 65 wherein the antibody comprises a detectable label.

67. The kit according to claim 66 wherein the detectable label is selected from the group consisting of fluorophores, radioactive isotopes, chromophores, and magnetic particles.

68. The kit according to claim 67 wherein the label moiety is detected by fluorescence activated cell sorting.

69. The kit according to claim 65 wherein the label moiety is detected by a third antibody.

70. The kit according to claim 69 wherein the label moiety is coupled to digoxigenin and the third antibody is specific for digoxigenin.

71. The kit according to claim 69 wherein the third antibody comprises a detectable label.

72. The kit according to claim 65 further comprising a biological modifier.

73. The kit according to claim 56 further comprising a cell-cell cross-contamination reducing capture system.

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